

Chapter 2

What Was Synthetic Biology?

Abstract The desire to make life is not new. Mythology and history provide numerous examples of this Promethean longing. Materialist and evolutionist scientists over a century ago were convinced of the possibility and even the need to synthesize living beings to advance the knowledge on the nature and origin of life. The premature synthetic biology attempts by Stéphane Leduc and Alfonso L. Herrera reflected the mechanistic ideal in biology of Jacques Loeb. The book “La biologie synthétique” by Leduc (1912) clearly defines the efforts of these pioneers: “Why is it less acceptable to seek how to make a cell than how to make a molecule?” Journalists have presented many advances in biology in the past century as an attempted synthesis of life. Nor is it new, therefore, the fine line which separates the scientific enthusiasm from hype.

The twentieth century may have witnessed the expansion and consolidation of biology in its myriad fields and many levels, ranging from molecular biology to ecology; however, the fundamentals of biological science date back to the previous century. It was in the nineteenth century that cell theory was developed, and Gregor Mendel, Louis Pasteur and Eduard Buchner performed their experiments; evolutionary theory was also put forward by Charles Darwin in the 1800s. In short, the nineteenth century marks the beginning of the materialistic study of living things. Thenceforth, life gradually broke away from the supernatural explanations that had escaped the realms ruled by the laws of physics and chemistry and lay beyond the bounds of the scientific method. The aspirations and intentions of those late nineteenth and early twentieth-century scientists were based on the belief that life could only have material explanations, and that they would only be able to understand it if they managed to make life in the laboratory.

2.1 Life and Matter

In 1868 Thomas Henry Huxley, personal friend and public champion of Darwin, gave a lecture entitled *On the physical basis of life*. Therein, Huxley referred to “protoplasm”, a proteinaceous material harbouring all the properties of living things, as an object of study *par excellence*, the true physical basis of life which could be studied thanks to advances in “molecular physics”. “[...] what community of form, or structure, is there between the animalcule and the whale; or between the fungus and the fig-tree? And, *a fortiori*, between all four? [...] if we regard substance, or material composition, what hidden bond connects the flower which a girl wears in her hair and the blood which courses through her youthful veins?” Huxley supported a view that not everyone shared at the time, namely that life was inseparably linked to matter and subject to physical laws and, although it might be at odds with common sense, “the physical basis or the matter of life was what united all living beings”, namely, that sort of proteinaceous matter that was common to them all: protoplasm. Moreover, the properties of protoplasm would be the “product of a certain disposition of material molecules.”

Then, in his 1870 speech as president of the British Association for the Advancement of Science, entitled “*Biogenesis and abiogenesis*” Huxley took a stronger intellectual stand. He acknowledged that life may have originated in the past from natural causes and did not rule out the possibility that life could be reproduced in the future, if the conditions enabling matter to acquire “vital” properties could be artificially established. Forty two years later, the president of the same Association, physiologist Sir Edward A. Schäfer, was to proclaim that the boundary between living and nonliving matter was so hazy that the only way to study the life phenomenon would be “by the same methods as all other phenomena of matter, and the general results of such investigations tend to show that living beings are governed by laws identical with those which govern inanimate matter”. Schäfer entertained the idea of synthesizing some of the major components of the cell, Miescher’s nuclein (our nucleic acids) and proteins, and did so with a very simplistic view built on the knowledge of cell chemistry in his day, which was somewhat inconsistent at the time. Schäfer finally stated his belief that life would be created in the laboratory: “The elements composing living substance are few in number [...]. The combination of these elements into a colloidal compound represents the chemical basis of life; and when the chemist succeeds in building up this compound it will without doubt be found to exhibit the phenomena which we are in the habit of associating with the term ‘life’ [...] The above considerations seem to point to the conclusion that the possibility of the production of life—i.e., of living material—is not so remote as has been generally assumed”. Thus, the debate at that time was no longer whether life could be synthesized or not, but rather *when* this scientific breakthrough would be made.

Jacques Loeb provides the best example of the mechanistic ideal and the experimentalist endeavour in biology (Pauly 1987). Before moving to the USA, Loeb had worked with some of the most advanced scientists of his time in both

physiology and chemistry: Adolph Fick, Julius Sachs and Svante Arrhenius. In 1896 Loeb explained his plans to set up a physiology laboratory at the University of Chicago. The laboratory—he said—would transform our view of nature and provide the following “services” to medicine: deal with the problem of famine, experimentally test the Darwinian explanation of the transformation of species, and “the most fundamental task of Physiology” was “whether or not we shall be able to produce living matter artificially”. Thus, according to Loeb, they could not only demonstrate the validity of physiologists’ ideas about biological phenomena, but also confirm the insignificance of beliefs in supernatural phenomena and, in doing so, convince the public they should trust in experimental scientists to direct social change. His positivist optimism led him to believe that science held the keys to progress, which could touch on all areas of human activity; a progressive science with unlimited prospects, even able to make life itself.

In 1906 Loeb published *The dynamics of living matter* which concluded by considering what the author deemed to be the two main issues facing biology: how to transform inert matter into living matter and how to transform a plant or animal species into another species. Loeb believed that the time had come to tackle these issues empirically and try to solve them. He was in favour of Pasteur’s germ theory, rejected spontaneous generation (or heterogenesis) and criticized its proponents. Likewise, he did not accept that synthesizing proteins was equivalent to creating life or obtaining life-like forms. Thus he stated plainly that the aim to synthesize life would not be achieved by simply obtaining the substance of living beings (albuminoids, colloids...) but by obtaining a mixture of these substances that would possess life-like characteristics (self-preservation, growth and reproduction). He said the outer shape was secondary, thereby distancing himself from some experimental attempts to synthesize life, which we will refer to later. In his work of 1912, eloquently entitled *The mechanistic conception of life* (Fig. 2.1) Loeb set out to analyze life from a strictly physicochemical view and stated that “we must either succeed in producing living matter artificially, or we must find the reasons why this is impossible”.

Loeb was what you might call a “visible scientist” in terms of media impact, but curiously he never actually tried to make living matter in the laboratory. However, he did become greatly renowned for achieving artificial parthenogenesis. In fact, he managed to make unfertilized sea-urchin eggs develop by simply changing the chemical composition of the surrounding medium. He was, therefore, able to replace the sperm with a chemical agent, which was taken to mean that biological processes must have a purely chemical basis. However, journalists at the time reported these experiments to be a real chemical creation of life, and some young ladies stopped bathing in the sea in case they got pregnant. Indeed, there was so much media hype that he felt obliged to publish a short note in the journal *Science*, in which he warned: “In view of the fact that a number of daily papers have printed reports concerning alleged or real experiments of mine I wish to state: (1) That none of the statements printed in the newspapers have been authorized by me. (2) That whatever I may have to say about my work will be published in scientific journals.”

Loeb continued his quantitative experimentation, and rounded off his vastly diverse (artificial parthenogenesis, ion transport across cell membranes, animal

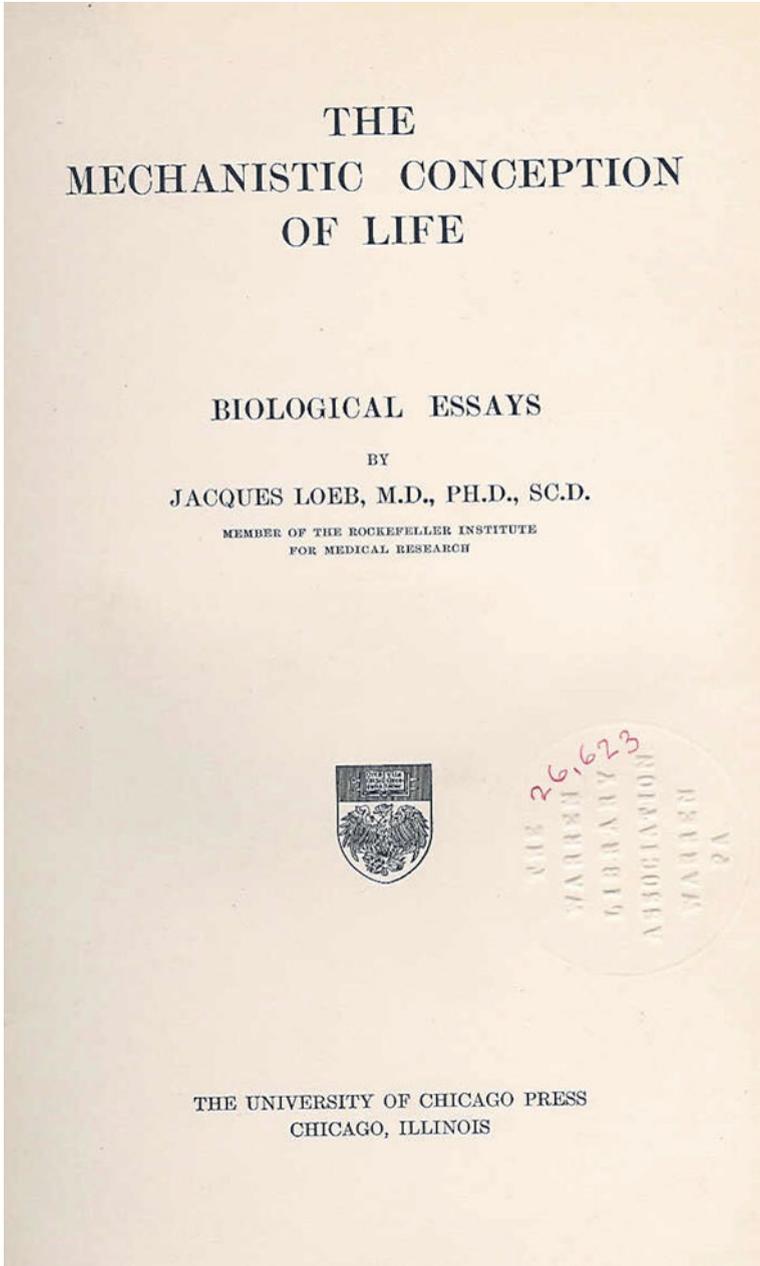


Fig. 2.1 Cover of Jacques Loeb's *The Mechanistic Conception of Life. Biological Essays* (1912)

tropisms) and distinguished career with a splendid study on proteins. His research helped to put an end to the idea held at the time that these cellular components did not obey the laws of chemistry. Thus, in the 1920s, scientists began to define the macromolecular nature of proteins and their physicochemical behaviour. Proteins were about to leave behind the domain of colloids, and biochemistry was to wake from what has been called “the dark age of biocolloidology”. In the early twentieth century, the colloidal state—consisting of tiny molecules—was proposed to bridge the gap between chemistry and biology. However, new physical techniques made it possible to measure the size of biological molecules and to crystallize proteins, while structural methods based on X-ray diffraction revealed images of giant molecules (macromolecules), which could not possibly fit with colloids (Morange 2003). Discoveries about the chemistry of biological macromolecules also contributed to pointing scientists away from seeking the essence of life in its form rather than in its chemical composition, and to contemplate life as a result of the crystallization of inanimate materials, as we shall see later.

2.2 Spontaneous Generation

Even before Jean-Baptiste Lamarck—forerunner of evolutionary ideas—, spontaneous generation was recognized as an additional reproductive mechanism to sexual reproduction. Aristotle described it for many plants and animals, and even in Shakespeare’s Mark Antony (*Antony and Cleopatra*) the mud of the Nile breeds life by action of the Sun. Many medieval legends believed in spontaneous generation and the existence of the so-called “goose-tree”, which gave rise to fish or birds depending on whether its seeds fell into the water or onto land, causing Pope Innocent III to explicitly prohibit the consumption of geese and ducks during Lent given the popular belief of their origin. Francesco Redi’s experiments in the seventeenth century, and the eighteenth-century controversy between Needham and Spallanzani, demonstrated spontaneous generation of animals to be impossible and shifted the belief in this process to the newly discovered microscopic world.

The pre-Darwinian view of nature was that all living beings were placed on the infinite rungs of a ladder leading up to heaven: The Great Chain of Being. The lower rungs held the minerals, progressing up through plants and humbler animals, such as worms, to the penultimate step where man was placed, preceded only by the angels on the stairway to God’s kingdom (Fig. 2.2). Carl Linnaeus, who introduced the current system of binomial nomenclature, devoted his life to putting each and every living being in its place, each one shaped and designed by the Creator. Then in the early nineteenth century, Lamarck began to shake the ladder, and thus worms might become men. Every living being was driven towards achieving perfection, which, together with the use or disuse of organs, made organisms evolve. Through evolution, living beings on the lower rungs could move a step up. But where did the beings on the first step come from? Following the noble precedent of the Count of Buffon, Lamarck proposed that the simplest life forms, at the base of the ladder,



Fig. 2.2 The great chain of Being or the Lullian staircase. *De noua logica, de correllatiuis, necnon [et] de ascensu [et] descensu intellectus* by Ramon Llull (published in València, 1512 by J. Costilla). Reproduced with permission of Historical Library, University of València, ref. BH R-1/341(1)

appeared through spontaneous generation. Thus, for the first time spontaneous generation was envisaged not as an alternative reproductive mechanism to sexual reproduction, but as an explanation for the very origin of life.

In 1859, coinciding with the publication of Darwin's book *On the Origin of Species*, Félix Pouchet published his *Hétérogénie ou traité de la génération spontanée basée sur de nouvelles expériences*, an extensive treatise which claimed to demonstrate spontaneous generation through numerous experiments. Such was the impact of the work that the French Academy of Sciences convened an award for scientists to demonstrate the existence, or not, of spontaneous generation. Finally, in 1862, the prize was won by the already famous chemist Louis Pasteur, for a series of brilliant and immaculate experiments showing the mistakes made by Pouchet. Although—strictly speaking—Pasteur did not repeat Pouchet's experiments and, therefore one might argue it was not a rigorous scientific rebuttal, the methods and instruments devised by Pasteur have gone down in history as one of the most remarkable examples of scientific reasoning. Pasteur in France and, later, John Tyndall in Britain—confronting Henry C. Bastian—almost managed to dismantle the ancient belief in spontaneous generation with the help of experimental scientific methods. However, as we shall see later, several authors attempted to skirt around Pasteur and Tyndall's hurdles.

2.3 The Synthesis of Living Beings a Century Ago

The definition of synthetic biology in the late nineteenth and early twentieth century revolved around the idea of making living things from purely physical and chemical ingredients. This concept could be traced back to two authors of reference: France's Stéphane Leduc and Mexico's Alfonso L. Herrera (Peretó and Català 2007). Leduc was professor of biophysics at Nantes medical school and was considered to be the main exponent of synthetic biology in Europe. He gained popularity for his work on osmotic growths in his day and was an author of reference for D'Arcy Thompson; however, he left very few traces of his scientific activity behind. Although his efforts to synthesize life may seem absurd today, as the historian and philosopher of science Evelyn Fox Keller recognizes, they constitute "an episode in the history of biological explanation, the ambitions those efforts reflected, as well as the interest they evoked in their time (Fox Keller 2002)".

Leduc thought, as did Loeb and Herrera, that there was continuity between the inanimate world and living beings, and that an understanding of the underlying biological mechanisms could be gained through synthesis. The year 1901 marks one of Leduc's first publications, a communication at the Congress of the French Association for the Advancement of Science in Ajaccio, entitled *Cytogenèse expérimentale*. Herein Leduc described how to synthesize cells and concluded that these artificial cells were identical in shape to living cells, and had the same organs, nucleus, cytoplasm, envelope membranes, as well as their main functions, cell metabolism and evolutionary capacity. He claimed that his experiments refuted two doctrinal

statements: the first proclaiming it impossible for living matter to be organized under the sole influence of physicochemical forces; and, the second stating that a cell cannot form spontaneously, and that every cell originates from a previous cell. Thus, in one foul blow, Leduc struck at vitalism and the impossibility of spontaneous generation, which were two of the cornerstones in the work of scientists like Pasteur.

After numerous communications to the Academy of Sciences, which sparked passionate debate among his colleagues and received some sharp and devastating criticism, Leduc undertook what would be his most outstanding work in the mechanistic study and experimental exploration of living matter. This was a series of three books entitled *Études de Biophysique* published between 1910 and 1921, of which the second volume was called *La biologie synthétique* (1912) (Fig. 2.3). This most probably marks the first time the term *Synthetic Biology* was used in a scientific work (Peretó and Català 2007; Campos 2009). Leduc's main proposal was that osmotic pressure was the only physical force required to generate amazing organic forms. The scope of synthetic biology ranged from the synthesis of organic molecules—fully consolidated through nineteenth century organic chemistry—including the synthesis of cells and tissues, to more complex structures. But Leduc wondered why organic synthesis was so well established and generally accepted while other stages were not only neglected but often treated with disdain. “Why is it less acceptable to seek how to make a cell than how to make a molecule?” Leduc wondered.

ÉTUDES DE BIOPHYSIQUE

LA BIOLOGIE SYNTHÉTIQUE

PAR
STÉPHANE LEDUC
PROFESSEUR A L'ÉCOLE DE MÉDECINE DE NANTES

AVEC 112 FIGURES DANS LE TEXTE



A. POINAT, ÉDITEUR
121, BOULEVARD SAINT MICHEL 4 PARIS
1912

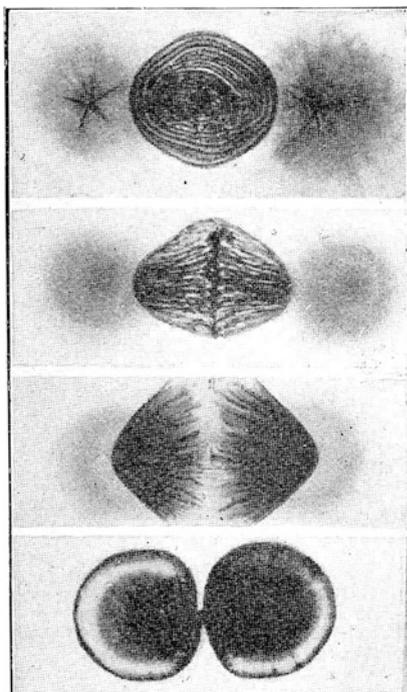


Fig. 2.3 Left Cover of Stéphane Leduc's *La biologie synthétique* (1912). Right Detail of figure on page 125 “four successive periods of karyokinetic division reproduced by diffusion”

This French scientist regretted the lack of attention paid to synthetic biology by academia, which considered his interpretations so fanciful that they could not possibly be taken seriously; however, his work gained great popularity with the lay public. The spectacular nature of osmotic growths, also known as chemical gardens, gained them access to a great many living rooms in the form of family entertainment. Leduc himself claimed that it was a wonderful sight to see a shapeless piece of calcium salt turn into a shell, coral or fungus, and all as a result of simple physicochemical forces. The anticipation and emotions stirred up by the fans of these chemical experiments have been immortalized in Thomas Mann's novel *Doctor Faustus*. The narrator describes the atmosphere created when onlookers contemplate the strange forms resulting from experiments made by Jonathan (father of the musician Adrian Leverkühn): " 'And even so they are dead', said Jonathan, and tears came in his eyes, while Adrian, as of course I saw, was shaken with suppressed laughter. For my part, I must leave it to the reader's judgment whether that sort of thing is matter for laughter or tears."

Leduc's work caused a stir even before his books were published. In 1902 the journal *The Academy and Literature* referred to a communication made by Leduc at the aforementioned Congress of Ajaccio, in which he explained his work of synthesizing cells from various chemicals. The commentator praised these efforts, linking them with speculation about the origin of life, adding that if they were well-founded, "the homunculus of Paracelsus, although it may never come to us in visible form, yet may not be such an impossible dream".

In all truth, the many illustrations showing the results of Leduc's experiments (like plant or fungal forms, cells dividing...) are of great beauty, and it is quite understandable that they should stir great public interest given their remarkable resemblance to living forms. Leduc's work is a nice example of how inorganic structures may strikingly resemble biological morphologies and textures (for further discussion on biomimetic materials, see below).

On the other side of the Atlantic, in Mexico, the prominent biologist Alfonso L. Herrera was a driving force behind several institutions introducing an evolutionary approach to the study of biology. Herrera is perhaps better known as the father of what he called *Plasmogenia*, a science aiming to synthesize life in the laboratory based on inorganic materials and which would unravel the enigma surrounding the origin of life, among other questions. His conviction that there was absolute continuity between inert matter and living matter is clearly expressed in what is considered the first Mexican biology text book: *Nociones de biología* (1904) "live pseudo-beings and pseudo-organized structures have been made in the laboratory, using reagents that are neither mysterious nor divine [...]. Indeed, they are so suggestive of analogies between animate and inanimate matter that the spirit is confused [...] and hesitates before drawing the final and definitive conclusion that *there is no separation between living forms and crystallized forms*". Two years later, his book was published in French under the title *Notions générales de biologie et plasmogénie comparées*.

Herrera published his unstinting work on Plasmogeny in the *Bulletin du Laboratoire de Plasmogenie* that he edited himself. In 1932 he contributed to a

biochemistry would temporarily move priorities away from scientists' dreams of synthesizing artificial life. For these critics, wishing to reduce life to its physico-chemical material basis may be legitimate; however, the way forward was not by using simple inorganic matter, as Leduc and Herrera did, but through colloids and proteins, which were beginning to reveal themselves to be giant molecules that were more difficult to study (Deichmann 2012). Therefore, studies should first endeavour to thoroughly characterize and seriously investigate the biochemical basis of life. Future advances were to show that not only should attention be paid to proteins—the true driving force of cell activity—but also to nucleic acids, which would take the driver's seat after the genetic studies of the 1940s. And later still, a third ingredient was to be added to attempts to reconstruct the simplest cell: the membranes formed by amphiphilic molecules.

Although we now know that the processes underlying the generation of those mineral, inorganic structures and life forms are quite different, the classic problem of studying the origins of natural structures through their morphological features is still unresolved. Indeed, establishing the biogenicity of structures—namely the chemical and/or morphological signature of past life—in the oldest geological records (i.e. microfossils and stromatolites) is a challenging and controversial topic. Likewise note that microscopic forms found in the Martian meteorite ALH84001 were interpreted by some as microfossils, an extraordinary claim that remains unproven. These are vivid examples of how this issue is still of great relevance to

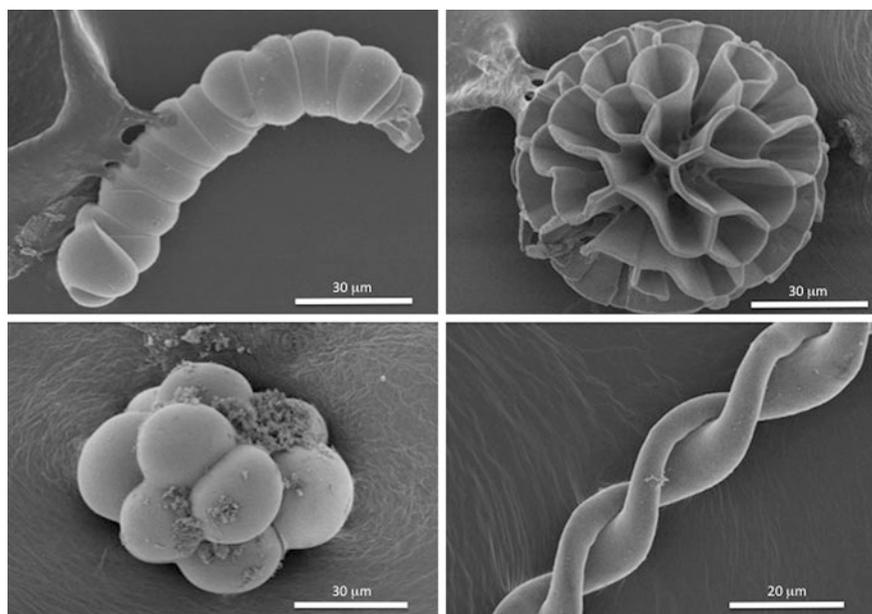


Fig. 2.5 Silica biomorphs. These microscopic objects self-organize by slow crystallization of barium carbonate in silica polymers at alkaline pH. Micrographs courtesy of Juan Manuel García-Ruiz (CSIC, Granada)

science today, namely, a key to dating of the origin of life and to identifying extraterrestrial life forms. The study of biomimetic chemical structures that self-organize under specific environmental conditions is an active research field in material science and biomineralization. Silica gardens (à la Leduc) and silica biomorphs (Fig. 2.5) are outstanding examples of these phenomena. Silica biomorphs offer a wonderful variety of elaborate morphologies with smooth curvature, very reminiscent of biological forms (Fig. 2.5).

2.4 Creating Life: Utopia and Propaganda

This idea of creating life artificially would resound among scientists and journalists throughout the twentieth century. The former perceived it as a far-off utopia, the latter as an achievement worthy of front-page headlines. So it was the Russian biochemist Aleksandr I. Oparin who linked the study of the origin of life with the experimental reproduction of the first steps in the evolutionary process. Oparin embodies the triumph over the scientific conflict and intellectual tension caused by accepting Darwinian evolution—with all its implications—and by acknowledging the irrefutable impossibility of spontaneous generation—as demonstrated by Pasteur and Tyndall. To be an unwavering Darwinian, meant admitting that all living things have a common origin and that, consistent with the rest of evolutionary theory, the origin of life could be traced back to purely material causes. According to Oparin, life originated as a result of a process of chemical evolution on a primitive Earth, where the right components, ingredients and physical conditions coincided, giving rise to the first elementary cells. In his first work, dating back to 1924, Oparin adopted an eclectic position that would allow biochemical innovations to be incorporated to his explanatory outline.

Although his 1924 pamphlet in Russian was not translated into English until 1967, his more comprehensive treatise published in 1936 took just 2 years to come out in English, and became widely known and readily accepted. This book begins with a rational argument against spontaneous generation and panspermia. The Russian author then went on to give a detailed explanation of the origin of life by chemical evolution. Oparin believed that it was legitimate to culminate experimental research on the origin of life by synthesizing life in the laboratory, stating: “the road ahead is hard and long but without leads to the ultimate knowledge of the nature of life. The artificial building or synthesis of living things is a very remote, but not unattainable goal along this road”.

The work by Stanley L. Miller and Harold C. Urey, who managed to simulate the primitive prebiotic synthesis of organic molecules in 1953, was reported in the media as a step towards synthesizing life. At the University of Chicago, Miller and Urey had mixed gases that were thought to be components of the early atmosphere (hydrogen, methane, ammonia and water vapour) and subjected it to an electric current. After a few hours the condensate liquid—simulating primitive seas—changed colour, indicating it contained new substances. Subsequent analysis

identified amino acids identical to those that make up proteins. This work had a huge media impact and even led to a Gallup poll, asking Americans if they thought it would be possible “to create life in a test tube”. Only 9 % of respondents answered affirmatively while 78 % answered negatively and 13 % did not know what to think. Needless to say, there is a huge gap between the complex mixture of organic molecules and the simplest cell.

Despite the fact public opinion seemed little inclined to think it possible to artificially synthesize life—recognizing the enormous complexity and difficulty of the project rather than religious reasons—, journalists did not miss the next opportunity to bring Frankenstein’s ghost back to the front pages. This came about in 1955, with the artificial reconstruction of tobacco mosaic virus (TMV) by Heinz Fraenkel-Conrat and Roblay Williams, at the University of California at Berkeley (Creager 2002). These researchers managed to obtain infectious TMV particles simply by mixing pure protein from the virus with genomic RNA, which were not infectious separately (although shortly afterwards, the RNA was shown to be pathogenic on its own). While there is an obvious connection with the artificial synthesis of life—given some researchers thought viruses may be the earliest primitive life forms—this biochemical achievement was to be expected. Indeed, it was a logical consequence of the self-assembly capacity of macromolecules and the biological role attributed to each of the viral components, and did not have any direct connection with scientific issues on the origin or synthesis of life. However, we could extend this debate to include other questions, such as: Is a virus a living thing? Does the self-assembly of macromolecular components taken from a pre-existing virus actually count as synthesis? In any event, the University of California managed to win the media attention they sought.

It would be worth studying this desire to present breakthroughs in biochemical research as the synthesis of life in the laboratory. A desire shared by journalists and politicians alike. In his autobiography *For the Love of Enzymes: The Odyssey of a Biochemist*, Arthur Kornberg (Kornberg 1989) recounts how a hundred newspaper and television reporters flocked to the press conference convened at Stanford University in 1967 to announce the enzymatic synthesis of the genome of the PhiX174 virus in a test tube, just one more chapter in a long series of studies into DNA synthesis by Kornberg. This was the first synthesis of a DNA viral genome that turned out to be biologically active. Kornberg himself warned the Stanford press office to avoid using phrases like “synthesis of life in the test tube” at all costs. Despite these precautions, worldwide the mass media made allusions to the creation of life in the laboratory. The same day, President Lyndon B. Johnson was taking part in an event to celebrate the *Encyclopaedia Britannica* bicentenary at the Smithsonian Institution in Washington and, ignoring the text provided by the Stanford press office, said “What are you going to read about tomorrow morning? It is going to be one of the most important stories that you ever read, your Daddy ever read, or your Grand-pappy ever read... Some geniuses at Stanford University have created life in the test tube!”. Alistair Cooke hit the nail on the head, stating in the *Manchester Guardian Weekly*: “It is near enough to the truth to astound the layman, far enough away to annoy the expert”.

In more recent times, similar media hype has surrounded the work of scientists led by J. Craig Venter (see Chap. 4). Not lacking pretension, Venter presented his experiments shrouded in the mystique of life created in the laboratory. Doubtless, he himself has helped to build an image of someone who denies playing at God while behaving likewise. It may be true that the synthesis of a complete genome and its successful transplantation in a cell is a technological breakthrough; however, it is debatable whether the resulting cell is entirely artificial or whether, in fact, it is a mere imitation, a simple copy of life as we know it.

References

- Campos L (2009) That was the synthetic biology that was. In: Schmidt M et al (eds) *Synthetic biology: the technoscience and its societal consequences*. Springer, Dordrecht, Chap 2, pp 5–21
- Cleaves HJ, Lazcano A, Ledesma Mateos I, Negrón-Mendoza A, Peretó J, Silva E (2014) Herrera's 'Plasmogenia' and other collected works: early writings on the experimental study of the origin of life. Springer, New York
- Creager ANH (2002) The life of a virus. Tobacco mosaic virus as an experimental model, 1930–1965. The University of Chicago Press, Chicago
- Deichmann U (2012) Crystals, colloids, or molecules?: Early controversies about the origin of life and synthetic life. *Perspect Biol Med* 55:521–542
- Fox Keller E (2002) Making sense of life. Explaining biological development with models, metaphors and machines. Harvard University Press, Cambridge
- Kornberg A (1989) For the love of enzymes the odyssey of a biochemist. Harvard University Press, Cambridge
- Leduc S (1912) *La biologie synthétique*. A Poinat, Paris
- Morange M (2003) *Histoire de la biologie moléculaire*. La Découverte, Paris
- Pauly PJ (1987) *Controlling life* Jacques Loeb and the engineering ideal in biology. Oxford University Press, New York
- Peretó J, Català J (2007) The renaissance of synthetic biology. *Biol Theor* 2:128–130